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The relationship between melatonin level, oxidative stress, fatigue and sleep disorders in multiple sclerosis patients

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ABSTRACT

Aims: Our study aimed to investigate the relationship between oxidative stress and melatonin levels, sleep disturbances and fatigue in persons with MS (pwMS).

Methods: The study included 50 pwMS and 30 healthy controls. Levels of serum melatonin, glutathione peroxidase (GPx), superoxide dismutase (SOD), and malondialdehyde (MDA) were measured in both groups. Persons with MS (pwMS) were evaluated using the extended disability status scale (EDDS) while Pittsburgh sleep quality index (PSQI), Epworth sleepiness scale, insomnia severity index, fatigue severity scale and Beck depression scale were used for both groups.

Results: Persons with MS (pwMS) exhibited significantly higher sleep disturbances (p<0,001), PSQI score (p<0,001), sleep latency (p=0,014), insomnia severity (p=0,001), fatigue (0,001) and fatigue severity (p<0,001), and Beck depression scale scores (p<0,001) and SOD levels (p<0,001) compared to the control group, while exhibiting significantly lower levels of melatonin(p=0,004). In pwMS, patients who experienced difficulty sleeping had significantly lower melatonin levels compared to those who did not (p=0,049). In pwMS, the melatonin level showed a negative correlation with age (r=-0,341; p=0,015) and EDSS (r=-0,386; p=0,006). Persons with MS (pwMS) with fatigue had significantly higher EDSS (p=0,003), PUQI (p=0,001), Epworth sleepiness score (p=0,028) and insomnia scores (p=0,002), compared to those who didn't.

Conclusion: Our results showed that the melatonin levels were lower, presence of fatigue, and fatigue severity were higher in pwMS with sleep disorders than in those without sleep disorders. The frequent occurrence of fatigue(indirectly) and sleep disturbances in pwMS can be attributed to low melatonin levels.

Keywords: Multiple sclerosis, melatonin, sleep disturbances, oxidative stress, fatigue

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disorder with neuroinflammatory and neurodegenerative features, primarily characterized by multifocal inflammatory-demyelinating lesions within the central nervous system. Etiology-wise, though exact causality remains elusive, the pathogenesis is thought to involve a complex interplay of genetic predisposition and environmental factors.[1]

Regions with lower sunlight exposure tend to have a higher prevalence of multiple sclerosis (MS). Additionally, MS often exhibits a seasonal pattern in terms of the occurrence of flare-ups.[2] The pineal gland serves as a neuroendocrine transducer that receives photoperiodic information from both the retina and the circadian suprachiasmatic nucleus oscillator. Melatonin is thought to potentially contribute to the physiopathology of multiple sclerosis (MS) and is directly influenced by the effects of sunlight in individuals without MS.[3] Recent studies have revealed that oxidative stress may have a significant role in the pathophysiology of MS.[4] Numerous studies have demonstrated that melatonin serves as an antioxidant and regulates lipid metabolism in MS. Moreover, it is involved in immunomodulation, neuroprotection, and neurogenesis in the context of MS.[5] Melatonin exerts its effects in MS by regulating gene expression, influencing antioxidant defense systems, and stimulating the activities of various antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx).[5]

Sleep disorders are more commonly observed in individuals with MS compared to the general population.[6] The role of melatonin as a sleep regulator is well-established, and it is documented that sleep disturbances

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in MS may share common underlying mechanisms. These mechanisms include circadian rhythm disruptions caused by impaired visual pathways, leading to compromised melatonin secretion and reduced input to the suprachiasmatic nucleus. Additionally, increased levels of proinflammatory cytokines may contribute to the connection between MS and sleep disturbances.[7] In our study, we aimed to investigate the relationship between melatonin level and oxidative stress, and disease and sleep disorders in persons with MS (pwMS).

METHODS

The study was carried with the permission of the Atatürk University Medical Faculty Clinical Researches Ethics Committee (Date: 29.03.2018, Decision No: 02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. No financial or other conflict of interest was declared by the authors.

Patients eligible for this study were those who were referred to the MS outpatient clinic within the timeframe from April 2018 to September 2018. Inclusion criteria dictated that individuals had to be diagnosed with MS based on the 2010 McDonald criteria. Patients experiencing MS exacerbations, those with an accompanying disease that may be confused with MS (SLE, antiphospholipid antibody syndrome, Sjogren's syndrome, Behcet's disease, SSS vasculitis, Sarcoidosis, etc.), those under the age of 18, those who had an MS attack in the last 3 months, those using vitamin supplements or steroids in the last 3 months, patients with chronic heart, liver, kidney or lung diseases, patients with endocrine disorders (diabetes mellitus, thyroid and parathyroid disorders, adrenal, pituitary insufficiency), those with malignancy, those previously diagnosed with sleep apnea or primary insomnia, those with a previous psychiatric condition and associated medication use and those who did not agree to participate were excluded from the study. A total of 50 pwMS were recruited in the study. A non-patient second group consisting of 30 healthy volunteers was created. All participants filled in a voluntary consent form. Demographic characteristics (gender, age, marital status, educational status, duration of MS diagnosis, number of MS attacks, MS subtype, presence of another disease, use of medication, body mass index) were questioned in face-to-face interviews while extended disability status scale was used to evaluate the severity of the disease[8] and fatigue severity scale[9], Pittsburgh sleep quality index[10], Epworth sleepiness scale[11], insomnia severity index[12] and Beck depression scale[13] were used to assess sleep disorders among control and/or patient groups by an experienced neurologist.

After an overnight fasting period, venous blood samples were collected from both the participating patients and control subjects by skilled personnel between 08:00 and 09:00 in the morning. Following a 30-minute resting period, the centrifugation process was carried out at 4000 rpm for a duration of 10 minutes. Subsequent to centrifugation, the samples were preserved at a temperature of -80°C until the point of analysis.[14]

Melatonin (Biont, Cat No: YLA0321HU) was analyzed with the ELISA (enzyme-linked immunosorbent assay) method according to the standard protocol recommended by the manufacturer.

Superoxide dismutase was analyzed with the Cayman brand superoxide dismutase assay kit (catalog number: 706002).

Glutathione peroxidase was analyzed with the Cayman brand glutathione peroxidase assay kit (catalog no: 703102).

Malondialdehyde is a product of lipid peroxidation and measured based on the absorbance of the pink-colored adduct of MDA with thiobarbituric acid (TBA) at 532 nm 15.

Statistical Analysis

The statistical analysis was conducted utilizing the Statistical Package for Social Sciences (SPSS) (software version 20 for Windows (IBM SPSS Inc., Chicago, IL). The normal distribution of data was examined using the Kolmogorov-Smirnov test. For normally distributed numerical variables, the results were presented as mean±standard deviation, whereas variables not adhering to normal distribution were presented as median (min-max). Categorical variables were reported as numbers and percentages. To compare normally distributed numerical variables across groups, the Student's t-test and ANOVA test were applied. Conversely, the Mann Whitney U and Kruskal Wallis H tests were utilized to compare non-normally distributed numerical variables between groups. Categorical data were compared using the Chi-square test and Fisher's exact test where applicable. Pearson and Spearman's rank correlation analyses were employed to explore associations between data variables. Statistical significance was established at a p-value of<0.05.

RESULTS

Our study cohort comprised 80 participants, including 50 patients diagnosed with MS and 30 healthy controls. Notably, no statistically significant differences were discerned in terms of gender, age, body mass index, and other socio-demographic characteristics between

the patient and control groups (**Table 1**). The mean expanded disability status (EDSS) Scale score for pwMS was 2. Among individuals with MS, the prevalence of sleep disturbances was marked at 88% and fatigue at 44%, whereas the control group exhibited a prevalence rate of 46.7%, resulting in a substantial divergence between the two groups (p<0.001). In regard to the Pittsburgh sleep quality index (PSQI) score, the MS group yielded an average score of 11.5, whereas the control group's average score was 4, indicating a noteworthy distinction between the two groups (p<0.001). Sleep latency exhibited a significant increase within the patient group (p=0.014). A considerable variance in the severity of insomnia between the groups was evident (p=0.001); nevertheless, no significant distinction was observed in terms of the clinical categorization of insomnia (p>0.05) (**Table 2**). Daytime sleepiness was found in 32% (n:16) of pwMS. Fatigue severity was higher in patients with increased daytime sleepiness than in those without (p=0.007).

Table 1. Groups' socio-demographic characteristics

	MS n=50	Control n=30	All population n=80	p
Age (mean±SD)	35.2±10.6	35.7±9.5	35.4±10.1	0.819
Gender (n)				0.605
Female	38	21	59	
Male	12	9	21	
BMI kg/m² (Mean±SD)	26.0±4.6	25.7±5.4	25.9±4.9	0.840
BMI distribution (n)				0.724
Normal	23	17	40	
Overweight	14	7	21	
Obese	13	6	19	
Smoking (n)	11	5	16	0.963
Alcohol (n)	1	0	1	
Marital status (n)				0.980
Married	30	24	54	
Single	16	4	20	
Divorced	3	1	4	
Widow	1	1	2	
Educational background (n)				0.085
No	2	1	3	
≤8 years	24	3	27	
9-12 years	17	9	26	
>12 years	7	17	24	
Disease type				
RRMS	44	-	44	
SPMS	5	-	5	
PPMS	1	-	1	
Treatment agents				
Interferon β1-a	12	-	12	
Fingolimod	11	-	11	
Teriflunomide	7	-	7	
Interferon β1-b	6	-	6	
Glatiramer acetate	6	-	6	
Natalizumab	5	-	5	
Dimethyl fumarate	3	-	3	

MS: Multiple Sclerosis, RRMS: Relapsing-Remitting MS, SPMS: Secondary Progressive MS, PPMS: Primary Progressive MS

Table 2. Distribution of sleep scales in MS patients and the control group

	All population n=80	MS n=50	Control n=30	p
PSQI: median (min-max)	7.5 (0-26)	11.5 (2-26)	4 (0-13)	<0.001*
Sleep disturbance (n%)				<0.001*
No	22 (27.5)	6 (12)	16 (53.3)	
Yes	58 (72.5)	44 (88)	14 (46.7)	
Sleep latency median (min-max)	15 (2-60)	20 (5-60)	10 (2-60)	0.014*
Insomnia severity median (min-max)	4 (0-20)	5.5 (0-20)	2 (0-10)	0.001*
Clinically insignificant insomnia n (%)	58 (72.5)	33 (66.0)	25 (83.3)	0.261
Insomnia lower threshold n (%)	20 (25.0)	15 (30.0)	5 (16.7)	
Clinical insomnia n (%)	2 (2.5)	2 (4.0)	-	
Epworth sleepiness scale median (min-max)	4 (0-15)	3 (0-12)	4.5 (1-15)	0.074
Daytime sleepiness n (%)				0.750
Normal	54 (67.5)	34 (68.0)	20 (66.7)	
Normal but increased daytime sleepiness	19 (23.8)	12 (24.0)	7 (23.3)	
Increased but moderate daytime sleepiness	6 (7.5)	4 (8.0)	2 (6.7)	
Increased but moderate daytime sleepiness	1 (1.3)	-	1 (3.3)	
Increased but severe daytime sleepiness	-	-	-	

MS: Multiple sclerosis, PSQI: Pittsburgh sleep quality index

Fatigue was found in 44% (n:22) of the pwMS. Mean age (40.7±10.3 vs. 30.8±8.7; p=0.001), female gender ratio (95.5% vs. 60.7%; p=0.012), median MS duration (6.5 vs. 3; p=0.005) in patients with fatigue compared to those without fatigue was found to be high. In patients with fatigue, median EDSS (3.3 versus 1; p=0.003), median PSQI (13.5 versus 7.5; p=0.001), median insomnia severity (8 versus 3.5; p=0.002), The median Epworth sleepiness score (4.5 versus 2.5; p=0.028) was found to be high. The rate of clinical insomnia was found to be higher in patients with fatigue compared to those without it (9.1% versus 0%; p=0.017) (**Table 3**).

Clinical depression was found in 28% (n:14) of the pwMS. It was found that all those with depression were women (p=0.035). Age, BMI, MS duration, number of attacks and medication distribution did not differ significantly according to the presence of depression. Melatonin and oxidative stress parameters did not show an association in pwMS with depression compared to those without depression. Median PSQI score (15 versus 9.5; p=0.009), median insomnia severity (8.5 versus 5; p=0.045), median Epworth sleepiness score (4.5 versus 3; p=0.050) in pwMS compared to those without depression were found to be high.

Table 3. The relationship between fatigue and related scales in MS patients

	Fatigue		p
	No n=28	Yes n=22	
EDSS	1 (0-6.5)	3.3 (0-6)	0.003*
PSQI	7.5 (2-22)	13.5 (4-26)	0.001*
Sleep disturbance			0.318
No	5 (17.9)	1 (4.5)	
Yes	23 (82.1)	21 (95.5)	
Sleep latency	15 (5-60)	20 (5-60)	0.075
Sleep duration	7.7±1.3	7.3±1.7	0.497
Severity of insomnia	3.5 (0-13)	8 (1-20)	0.002*
Clinically insignificant insomnia	23 (82.1)	10 (45.5)	0.017*
Insomnia lower threshold	5 (17.9)	10 (45.5)	
Clinical insomnia	-	2 (9.1)	
Epworth sleepiness scale	2.5 (0-12)	4.5 (1-12)	0.028*
Beck depression invantory	10 (0-24)	13 (7-27)	0.06
Clinical depression			0.395
No	22 (78.6)	14 (63.6)	
Yes	6 (21.4)	8 (36.4)	

EDSS: Extended disability status scale, PSQI: Pittsburgh sleep quality index

The patient group exhibited a notably diminished melatonin level (p=0.004). The SOD level demonstrated a marked increase within the patient group (p<0.001) (**Table 4**). Furthermore, in both the patient and control groups, no significant correlations were identified between melatonin levels and GPx, MDA, or SOD levels.

Within the control group, no significant correlations were identified between melatonin and oxidative stress parameters, as well as age, BMI, EDSS, PSQI score, sleep latency, sleep duration, insomnia severity index, and Epworth sleepiness scale (**Table 5**). However, among pwMS, a negative correlation was observed between melatonin levels and both age (p=0.015) and EDSS score (p=0.006). Conversely, a positive correlation emerged between GPx levels and age (p=0.026), duration of disease (p=0.046), and EDSS score (p=0.007) (**Table 4**). Notably, a negative correlation was established between MDA levels and parameters such as PSQI (p=0.003), sleep latency (p=0.049), and insomnia severity index (p=0.001) (**Table 5**).

In the subgroup analysis involving overweight individuals, a distinct pattern emerged, underscoring a noteworthy diminution in melatonin levels among subjects diagnosed with MS as opposed to the control cohort (415.8 vs. 586.4; p=0.010). Moreover, the median SOD16 level exhibited a discernible elevation (0.58 to 0.48; p=0.012), concomitant with a heightened mean malondialdehyde (MDA) level in pwMS (31.6±3.1 vs. 27.4±1.9; p=0.004). Of particular note was the nuanced correlation unveiled between the presence of sleep disorders and melatonin concentrations within the patient cohort. Specifically, melatonin levels exhibited a significant decrease in pwMS grappling with sleep difficulties in contrast to those without such issues (674.1 vs. 429.1; p=0.049). Additionally, individuals manifesting heightened daytime sleepiness displayed a tendency towards lower melatonin levels, though this relationship failed to reach statistical significance (p=0.479).

Table 4. Relationship between melatonin, GPx, SOD and MDA values in MS patients and controls

	All Population (n=80)	MS (n=50)	Control (n=30)	p
Melatonin (ng/L) median (min-max)	483.1 (266.8-1272.1)	438.9 (266.8-1180.7)	599.3 (307.9-1272.1)	0.004*
MDA (nmol/ml) median (min-max)	29.53 (24.8-56.2)	30.2 (24.8-56.2)	28.2 (26.2-36.5)	0.136
GPx (nmol/ml) median (min-max)	15282 (1018.8-35658)	15027.3 (1018.8-25979.4)	15282 (2037.6-35658)	0.176
SOD (U/ml) median (min-max)	0.57 (0.25-0.82)	0.6 (0.38-0.82)	0.5 (0.25-0.68)	<0.001*

MS: Multiple sclerosis GPx: Glutathione peroxidase, SOD: Superoxide dismutase, MDA: Malondialdehyde

Table 5. Findings of melatonin and oxidative stress parameters

Variables	Control								MS							
	Melatonin		GPX		SOD		MDA		Melatonin		GPX		SOD		MDA	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Melatonin (ng/L)	-	-	0.029	0.878	-0.316	0.089	-0.124	0.513	-	-	-0.141	0.329	0.221	0.124	-0.145	0.315
GPX (nmol/ml)	0.029	0.878	-	-	0.284	0.129	0.292	0.118	-0.141	0.329	-	-	-0.006	0.965	0.050	0.731
SOD (U/ml)	-0.316	0.089	0.284	0.129	-	-	0.313	0.092	0.221	0.124	-0.006	0.965	-	-	0.058	0.689
MDA (nmol/ml)	-0.124	0.513	0.292	0.118	0.313	0.092	-	-	-0.145	0.315	0.050	0.731	0.058	0.689	-	-
Age (n)	-0.304	0.103	-0.118	0.533	0.102	0.592	0.093	0.625	-0.341	0.015*	0.315	0.026*	0.001	0.994	0.171	0.234
BMI (kg/m²)	0.104	0.585	-0.100	0.599	0.044	0.818	0.134	0.479	-0.259	0.070	0.277	0.072	-0.071	0.623	0.272	0.108
Duration of disease (year)	-	-	-	-	-	-	-	-	-0.241	0.092	0.280	0.046*	-0.158	0.273	-0.038	0.793
Number of attacks (n/per year)	-	-	-	-	-	-	-	-	0.192	0.181	-0.263	0.065	-0.007	0.961	0.124	0.390
EDSS (n)	-	-	-	-	-	-	-	-	0.386	0.006*	0.374	0.007*	-0.072	0.621	0.018	0.900
PSQI a (n)	-0.259	0.167	-0.288	0.123	-0.097	0.611	-0.156	0.410	-0.219	0.126	-0.030	0.837	-0.189	0.189	-0.406	0.003*
Sleep latency (n)	-0.120	0.527	-0.130	0.495	-0.333	0.072	-0.332	0.073	-0.054	0.707	0.014	0.921	-0.161	0.264	-0.280	0.049*
Duration of sleep (n)	0.065	0.733	0.249	0.184	-0.165	0.385	0.085	0.656	0.004	0.977	0.012	0.932	-0.118	0.413	0.111	0.445
Insomnia severity index (n)	0.066	0.727	0.184	0.329	-0.267	0.153	-0.394	0.031	-0.086	0.554	-0.032	0.827	-0.154	0.286	-0.442	0.001*
Epworth score (n)	-0.051	0.790	0.081	0.669	0.322	0.082	-0.019	0.922	-0.093	0.521	-0.044	0.763	0.159	0.269	-0.226	0.114

DISCUSSION

Multiple sclerosis (MS) is a chronic neurological disease that has a significant impact on daily life activities. Studies have consistently shown that pwMS often encounter difficulties with sleep, and the prevalence of sleep disturbances in this population is higher compared to the general healthy population.[17] Various studies have reported the prevalence of sleep disturbances in individuals with MS to be within the range of 42-65%. Similarly, the prevalence of daytime sleepiness among pwMS has been estimated to be approximately 10-40%.[18] In our study, the patient group exhibited a higher rate of sleep disorders according to the Pittsburgh sleep quality Index compared to the control group, with a rate of 88%. Daytime sleepiness was found similar to the literature, with a rate of 32%.

The pathophysiology of MS is not fully understood, but oxidative stress in MS is characterized by the excessive production of reactive oxygen species and decreased antioxidant defense mechanisms, are both known to be involved in the pathogenesis of MS.[19] The disruption of antioxidant systems or increased production of reactive oxygen species (ROS) can contribute to lipoprotein peroxidation in MS. Lipoprotein lipid peroxidation products are neurotoxic and possess proinflammatory properties, which may play a role in demyelination and axonal injury in MS.[20] Studies involving melatonin have yielded remarkable findings.[3,4] Melatonin has been shown to enhance the activities of SOD 16 and glutathione peroxidase (GPx), while inhibiting the activity of the pro-oxidative enzyme nitric oxide synthase (NOS). It has been reported that melatonin therapy can lead to a decrease in malondialdehyde levels.[21] MDA is the primary and extensively studied product of peroxidation of polyunsaturated fatty acids. Studies have reported a significant increase in lipid peroxidation products, including MDA, in the brain, plasma, and cerebrospinal fluid of individuals with MS.[20] Indeed, different studies have reported varying results concerning the levels of GPx in pwMS.[22] It has been reported that individuals with MS exhibit higher levels of SOD 15, catalase (CAT), and glutathione reductase (GR) compared to healthy controls.[22] In our study, it was observed that the level of melatonin was significantly lower in pwMS compared to the control group, which aligns with existing literature. Furthermore, the production of melatonin was found to be negatively correlated with age and the expanded disability status scale[23], indicating a potential relationship between melatonin levels, age, and disease severity in MS. These findings contribute to our understanding of the role of melatonin in MS and its potential implications for disease progression. Our findings are consistent with the existing literature in terms of melatonin levels, GPx, and SOD in pwMS. The study results indicate that there was no significant difference in GPx levels between the patient and control groups, although GPx levels were lower in the patient group. On the other hand, SOD levels were higher in the patient group compared to the control group, which aligns with previous research.[24] Free radicals directly or indirectly activate endogenous detoxification mechanisms. Increased cytokines increase the expression of SOD.[25] These findings contribute to the understanding of the antioxidant status and oxidative stress markers in pwMS and support the notion of altered antioxidant defense mechanisms in the disease. In our study, no statistically significant difference was observed in the mean serum MDA levels between pwMS and the controls.

Melatonin is indeed a key regulator of the sleep-wake cycle. In healthy individuals, exogenous melatonin can aid in initiating sleep and improve sleep quality in various clinical conditions. Recent studies have provided evidence suggesting that melatonin therapy may have a role in regulating sleep patterns.[26] A different study has proposed that melatonin may exert chronobiological effects on sleep. It suggests that melatonin release is associated with the onset, quality, and latent stage of sleep rather than total sleep time. This effect is thought to be achieved through the hypothermic effect and thermoregulation mechanism of melatonin.[27] In our study, melatonin levels were lower in pwMS who experienced difficulty sleeping compared to those who did not. In pwMS, no significant correlation was found between melatonin levels and PSQI and Epworth sleepiness scale scores, sleep latency, duration of sleep and insomnia severity. Our findings were consistent with the literature. There is a limited number of studies examining the relationship between oxidative stress markers and sleep disorders. MDA level was found to be negatively correlated with PSQI, sleep latency and insomnia severity index. Again, SOD and GPx levels were not found to be significantly correlated with PSQI and Epworth sleepiness scale scores, sleep latency, duration of sleep and insomnia severity. These findings can be explained by the fact that oxidative stress markers can be affected by different physiological and pathophysiological processes. It is widely believed that melatonin can enhance the gene expressions and/or activities of various antioxidant enzymes, including SOD[16], peroxidase, glutathione (GSH), and lipid peroxidase. By doing so, melatonin is thought to suppress oxidative stress.[21] In our study, melatonin levels did not exhibit a significant correlation with oxidative stress parameters in patient and control groups. In our opinion, this supports the fact that the antioxidant mechanism is affected not only by melatonin, but also by different endogenous processes.

Although the etiology of fatigue in multiple sclerosis is not clearly known, a multifactorial etiology is mentioned, including individual, environmental and developmental factors. It is reported that 50-90% of pwMS experience fatigue.[28] In our study, which showed that 44% of people with MS have fatigue, there was a positive correlation between fatigue severity scores and EDSS, PSQI, Epworth sleepiness score and Beck depression score. There was no significant relationship between depression and fatigue severity or presence.

Depression is the most common psychiatric disorder in MS. Studies have shown that depression scores are higher in female patients than in male patients.[29] In our study, in agreement with the literature, 28% of pwMS were found to have clinical depression and all those with depression were female. In our study, there was no association between melatonin in pwMS with depression compared to those without depression. PSQI score, insomnia severity and Epworth sleepiness score were found to be significantly higher in pwMS with depression compared to controls.

Sleep disorders are highly prevalent among individuals with MS, and the findings of our study indicate that melatonin levels are lower in pwMS compared to the control group. Furthermore, those with pwMS with sleep difficulties exhibited lower melatonin levels and higher fatigue severity compared to those without sleep difficulties. However, no significant relationship was observed between melatonin levels and sleep latency, sleep duration, insomnia severity and fatigue in pwMS. Additionally, melatonin levels did not appear to have a direct impact on the oxidant/antioxidant system in this context. Considering the relationship between MS and sleep disorders, it can be thought that the decreased melatonin levels observed in pwMS may contribute to the frequent occurrence of sleep disorders and thus increase fatigue.

CONCLUSION

Sleep disturbance and fatigue are common in pwMS and should be a priority among clinical evaluations. However, further research is needed to fully understand the complex interplay between melatonin, sleep disorders, fatigue, and the oxidant/antioxidant system in MS.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Atatürk University Medical Faculty Clinical Researches Ethics Committee (Date: 29.03.2018, Decision No: 02).

Informed Consent

Written free informed consent was obtained from all participants in this study.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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